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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: C01B 33/24, A61L 27/00, 25/00	A1	(11) International Publication Number: WO 98/08773 (43) International Publication Date: 5 March 1998 (05.03.98)
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(54) Title: SILICON-SUBSTITUTED APATITES AND PROCESS FOR THE PREPARATION THEREOF (57) Abstract <p>The present invention provides a synthetic silicon-substituted apatite or hydroxyapatite which comprises from 0.1 % to 5 % by weight of silicon. The silicon-substituted apatite or hydroxyapatite material may be used as a synthetic bone material for use in bone substitution, implants, fillers and cements, coatings for metallic implants, and for making hydroxyapatite-polymer composites. The silicon-substituted apatite is prepared by reacting a calcium salt or calcium hydroxide with orthophosphoric acid or a salt of orthophosphoric acid in the presence of a silicon-containing compound, the molar ratio of calcium ions to phosphorous-containing ions being from 1:0.5 to 1:0.7 and the molar ratio of calcium ions to silicon-containing ions being at least 1:0.2, whereby a precipitate of a silicon-substituted apatite is formed. On heating and/or sintering the silicon-substituted apatite at a temperature of from 500 °C to 1400 °C part or substantially all of the silicon-substituted apatite transforms to silicon-substituted hydroxyapatite.</p>		

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SILICON-SUBSTITUTED APATITES AND
PROCESS FOR THE PREPARATION THEREOF

5 The present invention relates to a silicon-substituted apatite and to a process for the preparation thereof.

 The apatite group of minerals are based on calcium phosphate, with naturally occurring apatite having a molar ratio of Ca/P of 1.67. Hydroxyapatite, 10 which has the chemical formula $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$, and hydroxyapatite - glass composites have been used in the recent past as skeletal reconstitution materials and it has been observed that bonding of these bioactive materials to living tissues is achieved 15 through a bone-like apatite layer formed on their surfaces in a body environment. Formation of a bone-like apatite layer on implant material thus plays a vital role in osseointegration of the implant.

 K. Hata et al., J. Am. Ceram. Soc., 78, 1049-1053 20 (1995) have shown that a bone-like apatite layer is formed on the surfaces of CaO and SiO_2 glass-ceramics in simulated body fluid. It is suggested by the authors that the mechanism of formation of the apatite layer comprises the dissolution of calcium and 25 silicate ions from the glass surface which helps the formation of an apatite layer with silicate ions providing nucleation sites. Another mechanism proposed by Hench et al., J. Biomed. Mater. Res., 2, 117, 1971 is that the pH of the surface of the implant 30 becomes alkaline due to dissolution of ions which in turn causes supersaturation resulting in the precipitation of a bone-like apatite layer. Other mechanisms have also been suggested, including the proposal by Li et al., J. Mater. Sci. Mater. Med., 35 3, 452, 1992, that dissolution of amorphous calcium

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phosphate from the glass creates a negatively charged surface which attracts calcium ions to the implant surface and finally forms an apatite layer.

5 Silicate sulphate apatite has been synthesised by a solid state method, K.S. Leshkivich et al., J.Mater. Sci. Mater. Med., 4, 86-94, 1993, and found excellent biocompatibility *in vivo* tests and this material has been suggested for use as a low-load bearing bone graft material.

10 Silicon has been shown, in small quantities, to have a significant effect on the development and growth of the hard tissue of living bodies.

15 EP-A-0 540 819 relates to calcium phosphate and calcium carbonate materials with antibacterial properties, in which these materials are used as a carriers for silver and silicon. JP-A-7165518 relates to an antibacterial inorganic powder. JP-A-7008550 relates to a hydroxyapatite material for use in surgical replacement which contains Ba, Bi, Zr, Sr or
20 Si to improve X-ray contrast. JP-A-60024848 relates to a tooth or bone repair composition comprising a mixture of apatite derived from the bones of fish or mammals and an oxide of Zr, Al, Si and Zn.

25 We have now developed a silicon-substituted apatite material which has a much higher bioactivity than that of pure hydroxyapatite and which may be used as a synthetic bone material.

30 Accordingly, the present invention provides a synthetic silicon-substituted apatite or hydroxyapatite which comprises from 0.1 to 5% by weight of silicon. By the term silicon-substituted is meant that silicon is substituted into the apatite crystal lattice and is not merely added, in contrast to the prior art. It is believed that the silicon
35 enters the lattice on the phosphate site. The silicon

- 3. -

is though to exist and/or substitute as a silicon ion or as a silicate ion.

The silicon-substituted apatite or hydroxyapatite material according to the present invention may be an essentially single phase pure material.

Preferably, the synthetic silicon-substituted apatite or hydroxyapatite comprises from about 0.1 to about 1.6%, more preferably from about 0.5 to about 1.0% by weight of silicon.

The present invention also provides for the preparation of a stoichiometric silicon-substituted apatite which, when heated and optionally sintered at a temperature of from about 500°C to 1400°C, for example at about 1200°C, produces an essentially single phase material with a crystal structure comparable to pure hydroxyapatite. The present invention therefore allows for the production of an essentially phase pure material of silicon-substituted hydroxyapatite, which contains substantially no impurity phases, such as calcium oxide or tricalcium phosphate (TCP).

The silicon-substituted apatite or hydroxyapatite material may be used as a synthetic bone material, including dental materials, for example for use in bone substitution, implants, fillers and cements, coatings for metallic implants, and for making hydroxyapatite-polymer composites.

In another aspect the present invention provides a process for the preparation of a silicon-substituted apatite, which process comprises reacting a calcium salt or calcium hydroxide with orthophosphoric acid or a salt of orthophosphoric acid in the presence of a silicon-containing compound, the molar ratio of calcium ions to phosphorous-containing ions being from about 1:0.5 to about 1:0.7 and the molar ratio of

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calcium ions to silicon-containing ions being at least about 1:0.2, whereby a precipitate of a silicon-substituted apatite is formed. Under these conditions it is believed that the silicon-containing compound
5 yields silicon-containing ions, such as silicon ions and/or silicate ions for example, which substitute in the apatite lattice.

The molar ratio of calcium ions to phosphorous ions is preferably from about 1:0.55 to about 1:0.65
10 and the molar ratio of calcium ions to silicon ions is preferably at least about 1:0.16.

The process of the present invention is advantageously carried out by reacting an aqueous solution comprising a calcium salt or calcium
15 hydroxide and a silicon-containing compound at a pH of from about 9 to about 13 with an aqueous solution comprising a salt of orthophosphoric acid at a pH of from about 9 to about 13. The calcium salt is preferably calcium nitrate and, in particular, calcium
20 nitrate 4-hydrate. The salt of orthophosphoric is preferably diammonium orthophosphate or triammonium orthophosphate. The pH of the aqueous solution of the calcium salt and/or the pH of the aqueous solution of the salt of orthophosphoric acid is preferably
25 adjusted using ammonia, for example concentrated aqueous ammonia. The preferred pH of each solution is about pH 11.

An alternative way of carrying out the process of the present invention comprises reacting an aqueous
30 solution of calcium hydroxide and a silicon-containing compound with an aqueous solution of orthophosphoric acid. The pH of the aqueous solution of calcium hydroxide is preferably from about 10 to about 14, more preferably about 12.3. The pH of the aqueous
35 solution of orthophosphoric acid is preferably from

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about 1 to about 3, more preferably from about 1 to about 1.5.

In each of the embodiments of the process of the invention the silicon-containing compound preferably
5 comprises a silicon salt, such as a silicon carboxylate. Advantageously the silicon-containing compound comprises silicon acetate and, in particular, silicon acetate 4-hydrate.

The precipitated silicon-substituted apatite may
10 be separated from the reaction mixture by, for example, filtration, and then washed and dried to result in a silicon-substituted apatite material. The dried filter cake material may then be powdered using conventional techniques.

15 The dried silicon-substituted apatite material may then be heated and optionally sintered using conventional techniques, for example at a temperature of about 1200°C. Upon heating, the silicon-substituted apatite material transforms to a silicon-substituted hydroxyapatite material, although some of
20 the material may decompose to a mixture of hydroxyapatite and calcium oxide or hydroxyapatite and tricalcium phosphate (TCP), depending on the chemical composition of the material. If formed, then
25 preferably substantially all of the TCP is α TCP. Ideally, little or no decomposition of the silicon-substituted apatite material occurs upon heating, thereby resulting in an essentially phase pure material of silicon-substituted hydroxyapatite. A
30 phase purity, as measured by X-ray diffraction, of at least 98% can be achieved, preferably at least 99%, more preferably approximately 100%. Because certain phases, for example TCP, are soluble in body fluids, a high phase purity is beneficial to the long-term
35 stability of the material. It will be appreciated,

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however, that a range of materials containing silicon-substituted hydroxyapatite in varying amounts may be prepared in accordance with the present invention depending on the concentrations of the various
5 reactants. For example, two phase materials comprising silicon-substituted hydroxyapatite and TCP or calcium oxide can still usefully be used and are intended to fall within the scope of the present invention.

10 The present invention will now be described further, by way of example, with reference to the following drawing, in which:-

Figure 1 shows the distribution of X-ray intensity for the hydroxyapatite material of Example 6
15 (discussed below).

The present invention will be further described with reference to the following Examples.

EXAMPLE 1

20

141.69g of calcium nitrate 4-hydrate was dissolved in 600ml of double distilled water. The pH of solution was adjusted to about 11.0 using a concentrated ammonia solution. 1200ml of double
25 distilled water was then added to the solution. The solution was filtered. 8.46g of silicon acetate 4-hydrate was added to the constantly stirred calcium nitrate solution. The solution was heated at about 65°C for about one hour, with stirring. Most of the
30 silicon acetate 4-hydrate dissolved in the solution and only a very little remained suspended in the solution. The solution was constantly stirred and cooled down to the pre-determined temperature of the experiment. The solution was named as Solution A.

35 47.54g of diammonium hydrogen orthophosphate was

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dissolved in 360ml of double distilled water. The pH of the solution was adjusted to about 11 using a concentrated ammonia solution. 480ml of double distilled water was then added to the constantly stirred solution. The solution was filtered. The solution was named as Solution B.

Solution B was added dropwise to constantly stirred Solution A at the predetermined temperatures of 3°, 25°, 60° and 90°C over a period of about 2 hours. The precipitates so formed (A,B,C and D, respectively) were each agitated at room temperature for one hour and left overnight. Each precipitate was filtered using a Buchner funnel and washed several times using double distilled water. The filter cakes were dried for about 20 hours in a drier at about 85°C in filtered air. The dried materials were powdered using a pestle and mortar.

The microstructures of the precipitates were studied using a JEOL 100 CX transmission electron microscope (TEM). Carbon coated 200 mesh copper grids were dipped in a dilute suspension of the precipitate and examined in the bright field mode at a magnification of 50000x using an accelerating voltage of 100 kV. The TEM micrographs indicated that the precipitate had a spheroidal shape when precipitated at 3°C and an increasingly acicular shape when precipitated at 60° and 90°C.

X-ray diffraction studies of powdered samples were performed using a Siemens D5000 diffractometer. Cu_{Kα} radiation ($K_{\alpha} = 1.5418 \text{ \AA}$) was used with a linear position sensitive detector and a nickel diffracted beam monochromator.

Fourier transform infrared Nicolet 800 spectrometer (FTIR) with a Mtech photoacoustic (PAS) cell was used to analyse the powdered samples. Spectra

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were obtained at 4 cm^{-1} resolution averaging 128 scans. The FTIR spectra of the samples precipitated at 3° and 25°C showed phosphate bands at 1085, 1030, 961, 600 and 563 cm^{-1} , carbonate bands at 1455, 1418, 1327 and 883 cm^{-1} and a hydroxyl band at 3567 cm^{-1} with a broad peak.

A GBC Integra XM sequential inductively coupled plasma spectrometer (ICPS) was used to analyse for calcium, phosphorous, silicon and other trace elements in the prepared apatites. The carbonate content in the dry powder of silicon substituted apatite was determined as carbon using a Control Equipment Corporation Model 240 XA CHN element analyser. The results are given in Table 1 below:

15

TABLE 1

Sample	Ca mg/kg	P mg/kg	Si mg/kg	Mg mg/kg	Na mg/kg	Al mg/kg	Fe mg/kg	Cu mg/kg	Ba mg/kg	Sr mg/kg	Carbonate mg/kg
A	450800	185200	10146	15.4	4.98	27.8	25.8	1.1	<0.2	65.5	12500
B	408800	181300	10748	67.5	24.0	21.3	22.2	<1.0	2.2	61.1	8000
C	417700	176200	8820	4.4	10.6	15.4	23.5	2.6	<0.2	66.3	7000
D	463100	182100	10330	3.4	18.7	22.5	26.7	2.1	<0.2	68.1	9000
HA at 3°C	35400	181000	34.0	18.2	106	13.6	<1.0	3.2	1.6	66.2	10000
HA at 90°C	344000	179000	81.5	17.8	54.9	155.0	<1.0	4.8	1.4	56.0	7000

HA = hydroxyapatite

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EXAMPLE 2

The procedure of Example 1 was repeated, using an amount of 4.23g of silicon acetate 4-hydrate.

5 Precipitation was again carried out at temperatures of 30, 25°, 60° and 90°C to form precipitates A, B, C and D.

The precipitates were subjected to ICPS analysis, and the results are given in Table 2 below:

10

TABLE 2

Sample	Ca mg/kg	P mg/kg	Si mg/kg	Mg mg/kg	Na mg/kg	Al mg/kg	Fe mg/kg	Cu mg/kg	Ba mg/kg	Sr mg/kg	Carbonate mg/kg
A	458200	191400	4526	7.8	191	23.6	20.0	<1.0	0.3	60.8	9000
B	469700	194200	4188	<1.0	30.4	20.2	33.3	1.2	<0.2	64.5	6000
C	433400	186600	4429	3.1	30.3	22.0	44.9	2.0	<0.2	64.6	6000
D	454700	185500	4820	1.8	44.9	28.6	25.9	<1.0	<0.2	65.3	7000

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EXAMPLE 3

The procedure of Example 1 was repeated, using amounts of 1.06g and 12.69g of silicon acetate 4-hydrate, respectively. The precipitations were carried out at 3°C to give precipitates A and B, respectively.

The precipitates were subjected to ICPS analysis and the results are given in Table 3 below:

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TABLE 3

Sample	Ca mg/kg	P mg/kg	Si mg/kg	Mg mg/kg	Na mg/kg	Al mg/kg	Fe mg/kg	Cu mg/kg	Ba mg/kg	Sr mg/kg	Carbonate mg/kg
A	424000	252000	1883	0.9	55.3	37.6	12.1	1.0	<0.1	63.6	11500
B	393000	268000	16101	10.3	64.9	10.5	24.6	0.8	3.6	67.9	16500

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EXAMPLE 4

44.46g of calcium hydroxide was dissolved in 600ml of double distilled water. 0.564g of silicon acetate 4-hydrate was dissolved in the calcium hydroxide solution. The solution was named as Solution A.

38.02g of orthophosphoric acid was dissolved in 360ml of double distilled water. The solution was named as Solution B.

Solution B was added dropwise to Solution A over a period of about 2 hours at a temperature of about 3°C. The precipitate so formed, designated precipitate A, was stirred for 1 hour and left overnight. Precipitate A was filtered using a Buchner funnel and washed several times using double distilled water. The filtered cake was dried for about 20 hours in a drier at about 85°C in filtered air. The dried material was powdered using a pestle and mortar.

This procedure was repeated, using amounts of 2.82, 5.64 and 8.46g of silicon acetate 4-hydrate. The precipitations were again carried out at about 3°C. to give precipitates B, C and D, respectively.

The precipitates A, B, C and D were subjected to ICPS analysis and the results are given in Table 4 below:

TABLE 4

Sample	Ca mg/kg	P mg/kg	Si mg/kg	Mg mg/kg	Na mg/kg	Al mg/kg	Fe mg/kg	Cu mg/kg	Ba mg/kg	Sr mg/kg	Carbonate mg/kg
A	424000	244000	814	41.0	48.4	17.5	24.6	0.5	2.6	2.9	50000
B	433000	240000	2957	31.4	115.3	18.8	27.1	<0.5	<0.1	2.1	45000
C	395000	250000	5337	27.5	54.7	22.3	28.4	0.8	<0.1	4.5	60000
D	390000	271000	5634	23.7	27.1	10.8	31.6	<0.5	<0.1	2.0	110500

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EXAMPLE 5

The silicon-substituted apatite material of Example 2A was pressed and sintered at about 1200°C at a heating rate of about 2.5°C/minute and a dwell time of about 4 hours at the final temperature. The
5 sintered sample was polished with diamond paper and a mirror-like surface was obtained. Hydroxyapatite was also pressed and sintered under the same conditions.

The samples were soaked in a simulated body fluid. After 1 day, thin film X-ray diffraction
10 spectra indicated that the sintered silicon substituted apatite material of Example 2A had formed a bone-like apatite layer, whereas the sintered hydroxyapatite formed a similar layer only after immersion in the fluid for 14 days.

15

EXAMPLE 6

36.671g of calcium hydroxide was dissolved in 1000ml of double distilled water. 1.917g of silicon acetate 4-hydrate was dissolved in the calcium hydroxide solution. The solution was named as Solution A.

33.331g of orthophosphoric acid (GPR 85% assay) was dissolved in 1000ml of double distilled water. The solution was named as Solution B.

Solution B was added dropwise to Solution A over a period of about 2 hours at a temperature of approximately 20°C. The pH of the mixture was adjusted to approximately 10.5 using a concentrated ammonia solution. The precipitate so formed, designated precipitate A, was stirred for 1 hour and left overnight. Precipitate A was filtered using a Buchner funnel and washed several times using double distilled water. The filtered cake was dried at about 85°C in filtered air. The dried material was powdered using a pestle and mortar.

The powder was then subjected to chemical analysis and the results are given in Table 5 below.

Next, the powder was heated at approximately 1200°C for about 2 hours and the phases present were determined using X-ray diffraction. With reference to Figure 1, the heated powder contained only one phase which matched the standard diffraction pattern for pure hydroxyapatite (Joint Committee for Powder Diffraction Standards, JCPDS Card no. 9-432).

The lattice parameters of the heated silicon-substituted hydroxyapatite were calculated from the diffraction data using a least squares refinement method. The values are listed in Table 6, along with the values for pure hydroxyapatite prepared by the above method, with 0.5 moles of Ca(OH)₂ and 0.3 moles

of H_3PO_4 , which does not contain any silicon. The increase in the lattice parameters is evidence of the substitution of silicon in the hydroxyapatite lattice.

Table 5

Sample	Ca mg/kg	P mg/kg	Si mg/kg	Mg mg/kg	Na mg/kg	Al mg/kg
A	381600	171900	3410	15	65	21

Sample	Fe mg/kg	Cu mg/kg	Ba mg/kg	Sr mg/kg	Carbonate mg/kg
A	32	2	0.2	62	5000

Table 6

	a-axis (nm)	c-axis (nm)
Pure hydroxyapatite	0.94159(1)	0.68798(1)
Single phase silicon-substituted hydroxyapatite prepared in accordance with the invention	0.94208(2)	0.68889(2)

CLAIMS:

1. A synthetic silicon-substituted apatite or hydroxyapatite which comprises from 0.1% to 5% by weight of silicon.
2. A synthetic silicon-substituted apatite or hydroxyapatite as claimed in claim 1 which comprises from 0.1% to 1.6% by weight of silicon.
3. A synthetic silicon-substituted apatite or hydroxyapatite as claimed in claim 1 or claim 2 which comprises from 0.5% to 1.0% by weight of silicon.
4. A synthetic bone material which comprises a synthetic silicon-substituted apatite or hydroxyapatite as claimed in any one of the preceding claims.
5. A synthetic bone material as claimed in claim 4 which comprises silicon-substituted hydroxyapatite and calcium oxide or tricalcium phosphate.
6. An essentially phase pure synthetic bone material of synthetic silicon-substituted hydroxyapatite as claimed in any one of claims 1 to 3 having substantially no impurity phases of calcium oxide and/or tricalcium phosphate.
7. A composition which comprises a synthetic bone material as claimed in any one of claims 4 to 6 together with a pharmaceutically acceptable diluent or carrier.

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8. A bone implant, filler or cement which comprises a synthetic bone material as claimed in any one of claims 4 to 6 or a composition as claimed in claim 7.

9. A hydroxyapatite-polymer composite material comprising a synthetic bone material as claimed in any one of claims 4 to 6 or a composition as claimed in claim 7.

10. A process for the preparation of a silicon-substituted apatite, which process comprises reacting a calcium salt or calcium hydroxide with orthophosphoric acid or a salt of orthophosphoric acid in the presence of a silicon-containing compound, the molar ratio of calcium ions to phosphorous-containing ions being from 1:0.5 to 1:0.7 and the molar ratio of calcium ions to silicon-containing ions being at least 1:0.2, whereby a precipitate of a silicon-substituted apatite is formed.

11. A process as claimed in claim 10, wherein the molar ratio of calcium ions to phosphorous-containing ions is from 1:0.55 to 1:0.65.

12. A process as claimed in claim 10 or claim 11, wherein the molar ratio of calcium ions to silicon-containing ions is at least 1:0.16.

13. A process as claimed in any one of claims 10 to 12, wherein an aqueous solution of a calcium salt and a silicon compound at a pH of from 9 to 13 is reacted with an aqueous solution comprising a salt of orthophosphoric acid at a pH of from 9 to 13.

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14. A process as claimed in any one of claims 10 to 13, wherein the calcium salt comprises calcium nitrate.

15. A process as claimed in any one of claims 10 to 14, wherein the salt of orthophosphoric acid comprises diammonium orthophosphate.

16. A process as claimed in any one of claims 13 to 15, wherein the pH of the aqueous solution of the calcium salt and/or the pH of the aqueous solution of the salt of orthophosphoric acid is adjusted using ammonia.

17. A process as claimed in claim 16 wherein the pH of each solution is adjusted to approximately 11.

18. A process as claimed in any one of claims 10 to 12, wherein an aqueous solution comprising calcium hydroxide and a silicon-containing compound is reacted with an aqueous solution comprising orthophosphoric acid.

19. A process as claimed in any one of claims 10 to 18, wherein the silicon-containing compound comprises a silicon carboxylate.

20. A process as claimed in claim 19, wherein the silicon carboxylate comprises silicon acetate.

21. A process as claimed in any one of claims 10 to 20, wherein the precipitated silicon-substituted apatite is separated from the solution and dried.

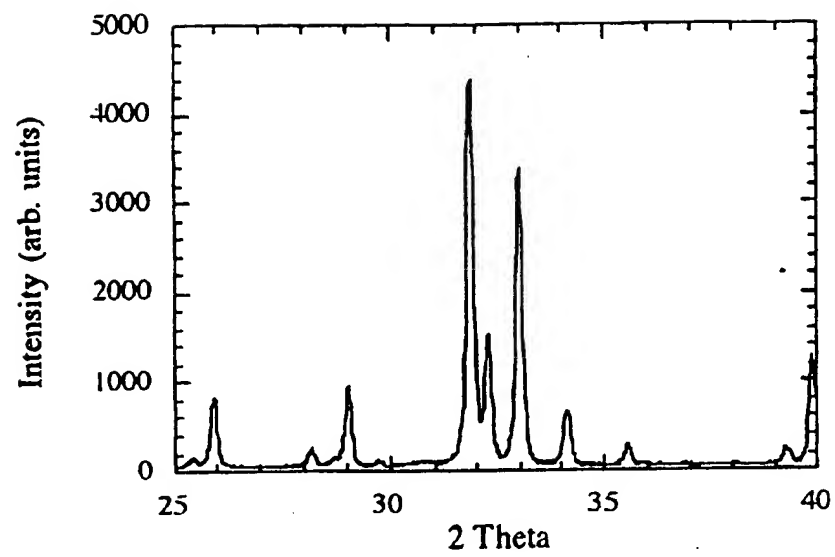
22. A process as claimed in any one of claims 10

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to 21, wherein the silicon-substituted apatite is heated and/or sintered.

23. A process as claimed in claim 22, wherein the silicon-substituted apatite is heated and/or sintered at a temperature of from 500°C to 1400°C, whereby part or substantially all of the silicon-substituted apatite transforms to silicon-substituted hydroxyapatite.

24. A synthetic silicon-substituted apatite or hydroxyapatite as claimed in any one of claims 1 to 3 or a synthetic bone material as claimed in any one of claims 4 to 7 for use in a method of treatment of the human or animal body by surgery or therapy.

*FIG. 1.*

INTERNATIONAL SEARCH REPORT

Int. J. Appl. No.
PCT/GB 97/02325

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C01B33/24 A61L27/00 A61L25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C01B

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YOSHIKI TANIZAWA & TAKASHI SUZUKI: "X-ray photoelectron spectroscopy study on silicate-containing apatite" PHOSPHOROUS RESEARCH BULLETIN, vol. 4, 1994, pages 83-88, XP002048627 see the whole document	1,4,6,8, 10,12, 21,24
Y	---	5,7,8
Y	EP 0 115 549 A (ETHICON INC) 15 August 1984 see claims 1-6 ---	5,7,8
	-/--	

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Date of the actual completion of the international search

3 December 1997

Date of mailing of the international search report

17/12/1997

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INTERNATIONAL SEARCH REPORT

Int. l. Application No

PCT/GB 97/02325

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